Supporting Information

Discovery of Potent Mcl-1 Inhibitors Using Fragment-Based Methods and Structure-Based Design

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Contents of Supporting Information

X-ray data collection and refinement statistics.

Protein						
Ligand	Cmp. 9	Cmp.10 /Cmp. 2	Cmp. 10 /Cmp. 8	Com. 20	Cmp. 49	Cmp. 60
PDB entry						
No. chains in sym. unit	12	1	1	1	4	4

Data collection

Space group	$P2_12_12_1$	$P2_12_12$	$P22_12_1$	$P2_12_12$	$P6_322$	$P2_1$
Cell dimensions						
a, b, c (Å)	79.94,152.79, 189.21	51.08,61.68,42 .30	42.21,51.32,61 .60	51.14,60.53,42 .23	150.16,150.1 6,121.58	35.04,115.0 0,95.32
α, β, γ (°)	90.00, 90.00, 90.00	90.00,90.00,90 .00	90.00,90.00,90 .00	90.00,90.00,90 .00	90.00,90.00,1 20.00	90.00,91.17 ,90.00
Resolution (Å)	50.00 – 3.0 (3.03 – 3.00)	50.00-1.60 (1.64-1.60)	50.00-1.50 (1.53-1.50)	50.00-1.41 (1.46-1.41)	50.00-2.80 (2.85-2.80)	50.00-2.60 (2.65-2.60)
R_{sym}/R_{merge}	10.8 (39.9)	4.2(38.9)/4.9(4 3.8)	5.3(29.9)/4.5(3 6.4)	4.8(38.3)/4.5(3 2.4)	9.7(49.7)/10.5 (51.1)	11.3(49.9)/ 10.5(46.4)
$I / \sigma I$	11.4 (2.4)	15.9(8.4)	12.5(4.9)	18.3(7.6)	4.7(2.5)	5.3(1.5)
Completeness (%)	85.9 (80.0)	94.1(92.4)	94.3(91.8)	97.8(94.3)	99.9(96.0)	94.9(91.3)
Redundancy	3.7 (2.9)	5.5(4.3)	7.5(2.7)	8.7(4.8)	8.1(3.4)	4.1(3.5)

Structure Refinement

No. reflections	48165	17166	20560	25366	20421	22089
R_{work} / R_{free}	17.72 / 25.41	17.82/21.80	12.06/18.18	15.70/19.73	24.60/29.32	22.23/30.09
RMS deviations						
Bond lengths (Å)	0.010	0.006	0.021	0.010	0.015	0.011
Bond angles (°)	1.559	0.959	1.831	1.445	1.801	1.515

Chemistry Experimental:

General. All NMR spectra were recorded at room temperature on a 400 MHz AMX Bruker spectrometer. ^{1}H chemical shifts are reported in δ values in ppm downfield with the deuterated solvent as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). Low resolution mass spectra were obtained on an Agilent 1200 series 6140 mass spectrometer with electrospray ionization. All samples were of ≥95% purity as analyzed by LC–UV/vis-MS. Analytical HPLC was performed on an Agilent 1200 series with UV detection at 214 and 254 nm along with ELSD detection. LC/MS parameters were as follows: Phenomenex-C18 Kinetex column, 50 x 2.1 mm, 2 min gradient, 5% (0.1% TFA/MeCN) / 95% (0.1% TFA/ H_2O) to 100% (0.1% TFA/MeCN). Preparative purification was performed on a Gilson HPLC (Phenomenex-C18, 100 x 30 mm, 10 min gradient, 5→95% MeCN/H_2O with 0.1% TFA) or by automated flash column chromatography (Isco, Inc. 100sg Combiflash). Solvents for extraction, washing, and chromatography were HPLC grade. All reagents were purchased from chemical suppliers and used without purification.

Preparation of acylsulfonamides:

General Procedure 1 (GP1): Direct Coupling to indole-2-carboxylic acids. To a stirred solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (**1**) (0.10 mmol) in CH_2Cl_2 (1.0 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.20 mmol), DMAP (0.30 mmol), Et_3N (0.30 mmol), and selected sulfonamide (0.11 mmol). The reaction mixture was stirred for 15 h at ambient temperature then concentrated *in vacuo*. The residue was dissolved in 1:1 mixture of CH_3CN/MeOH (1.0 mL) then filtered. The filtrate was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 95% CH_3CN 0.1% TFA) to give a corresponding acylsulfonamide in 25-85% yield.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-(methylsulfonyl)-1*H*-indole-2-carboxamide (9). Prepared according to **GP1** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (39 mg, 0.10 mmol) and methanesulfonamide (11 mg, 0.11 mmol). The title compound (36 mg, 0.078 mmol) was isolated as a white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.71 (d, J = 8.6 Hz, 1H),

7.54 (d, *J* = 0.9 Hz, 1H), 7.08 (dd, *J* = 8.6, 1.3 Hz, 1H), 6.74 (s, 2H), 3.92 (t, *J* = 6.3 Hz, 2H), 3.37 (s, 3H), 3.18 (t, *J* = 7.1 Hz, 2H), 2.27 (s, 6H), 2.10-1.96 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 469.1 $(M+H)^+$.

6-Chloro-*N*-(methylsulfonyl)-3-(3-(naphthalen-1-yloxy)propyl)-1*H*-indole-2-carboxamide (10). Prepared according to **GP1** from 6-chloro-3-(3-(naphthalene-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (38 mg, 0.10 mmol) and methanesulfonamide (11 mg, 0.11 mmol). The title compound (40 mg, 0.085 mmol) was isolated as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): 9.20 (s, 1H), 9.10 (s, 1H), 8.15 (m, 1H), 7.82 (m, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.51 (m, 3H), 7.41 – 7.34 (m, 3H), 6.83 (d, J = 7.6 Hz, 1H), 4.19 (t, J = 5.6 Hz, 2H), 3.43 (t, J = 6.8 Hz, 2H), 2.85 (s, 3H), 2.45 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 457.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-(methylsulfonyl)-1*H*-indole-2-carboxamide (11). Prepared according to **GP1** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (36 mg, 0.10 mmol) and methanesulfonamide (11 mg, 0.11 mmol). The title compound (30 mg, 0.069 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.57 (br s, 1H), 9.15 (br s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.45-7.35 (m, 2H), 7.19 (t, *J* = 4.0 Hz, 1H), 6.75 (s, 2H), 3.82 (t, *J* = 4.0 Hz, 2H), 3.34 (t, *J* = 8.0 Hz, 2H), 3.17 (s, 3H), 2.32-2.28 (m, 8H); >98% at 215 nm, MS (ESI) *m/z* = 435.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-phenoxyethyl)sulfonyl)-1*H*-indole-2-carboxamide (12): Prepared according to **GP1** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (36 mg, 0.097 mmol) and 2-phenoxyethane-1-sulfonamide (22 mg, 0.11 mmol). The title compound (27 mg, 0.054 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.66 (br s, 1H), 9.30 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.48-7.37 (m, 2H), 7.26-7.14 (m, 3H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.67 (s, 2H), 6.56 (d, *J* = 8.0 Hz, 2H), 6.45 (br s, 2H), 4.26 (t, *J* = 4, 2H), 3.90 (t, *J* = 6.0 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.28 (t, *J* = 6.0 Hz, 2H), 2.44-2.18 (m, 8H), 2.04 (s, 1H); >98% at 215 nm, MS (ESI) *m/z* = 541.2 $(M+H)^+$.

General Procedure 2 (GP2): *In situ* formation of amide/sufonamide bonds from acyl chlorides followed by acylsulfonamide coupling. To a stirred solution of 2-aminoethanesulfonamide hydrochloride (0.062 mmol) in CH_2Cl_2 (0.62 mL) was added

Et_3N (0.19 mmol) and selected acyl chloride (0.068 mmol) at 0°C. The reaction was stirred at 0°C for additional 30 min then warmed to ambient temperature and stirred for 15 h. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 mmol), DMAP (0.19 mmol), and of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (0.062 mmol) were added to the reaction then stirred for another 15 h. Upon completion the reaction mixture was concentrated *in vacuo* and the residue was dissolved in 1:1 mixture of CH_3CN/MeOH (1.0 mL) then filtered. The filtrate was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 95% CH_3CN 0.1% TFA) to give a corresponding acylsulfonamide in 15-45% yield.

***N*-((2-Benzamidoethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (13).** Prepared according to **GP2** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (22 mg, 0.062 mmol) and benzoylchloride (10 mg, 0.068 mmol). The title compound (8.3 mg, 0.031 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.65 (m, 1H), 7.70 (d, J = 8Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.46-7.41 (m, 2H), 7.32-7.28 (m, 3H), 7.08-7.04 (m, 1H), 6.74 (s, 2H), 3.90-3.73 (m, 6H), 3.43 (br s, 2H), 3.11 (m, 2H), 2.26 (s, 7H), 1.97 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 568.2 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(cyclohexanecarboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (14). Prepared according to **GP2** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (22 mg, 0.062 mmol) and cyclohexanecarbonyl chloride (10 mg, 0.068 mmol). The title compound (9.2 mg, 0.016 mmol)was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.64 (br s, 1H), 9.15 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.43-7.38 (m, 2H), 7.36-7.16 (m, 1H), 6.75 (s, 2H), 6.00 (t, J = 6.0 Hz, 1H), 3.89 (t, J = 6.0 Hz, 2H), 3.7-3.66 (m, 2H), 3.56-3.53 (m, 2H), 3.34 (t, J = 6.0 Hz, 2H), 2.33 (s, 6H), 2.29-2.23, (m, 2H), 2.01-1.94 (m, 1H), 1.79-1.71 (m, 4H), 1.58 (br s, 12H), 1.41-1.16 (m, 7H); >98% at 215 nm, MS (ESI) m/z = 574.2 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(2-cyclohexylacetamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (15). Prepared according to **GP2** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (22 mg, 0.062 mmol) and cyclohexylacetyl chloride (11 mg, 0.068

mmol). The title compound (5.5 mg, 0.0093 mmol)was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.59 (br s, 1H), 9.05 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.52-7.30 (m, 3H), 7.20-7.10 (m, 1H), 6.76 (s, 2H), 6.61 (s, 1H), 5.92 (s, 1H), 3.96-3.87, (m, 3H), 3.68-3.64 (m, 2H), 3.55-3.52 (m, 2H), 3.36-3.26 (m, 3H), 2.33-2.26, (m, 11H), 2.17-2.13 (m, 1H), 1.955 (d, J = 4, 2H), 1.72-1.65 (m, 6H), 1.28-1.11 (m, 5H), .87 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 588.3 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((3-(cyclohexylamino)propyl)sulfonyl)-1*H*-indole-2-carboxamide (16). 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((3-chloropropyl)sulfonyl)-1*H*-indole-2-carboxamide (30 mg, 0.060 mmol) was prepared according to **GP1** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (30 mg, 0.082 mmol) and 3-chloropropane-1-sulfonamide (13 mg, 0.082 mmol). It was directly used for the subsequent step.

To a stirred solution of 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((3-chloropropyl)sulfonyl)-1*H*-indole-2-carboxamide (30 mg, 0.060 mmol) in DMF (0.5 mL) was added $NaHCO_3$ (15 mg, 0.18 mmol), cyclohexylamine (9.0 mg, 0.090 mmol) and KI (cat. amount). The reaction mixture was stirred at 70 °C for 24 h. After cooling to ambient temperature, the reaction was quenched with H_2O and extracted with EtOAc (3 x 10mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in 1:1 mixture of CH_3CN/MeOH (1.0 mL) then filtered. The filtrate was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 95% CH_3CN 0.1% TFA) to yield the title compound (13 mg, 0.022 mmol) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.46 (s, 1H), 8.86 (br s, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.34-7.27 (m, 2H), 7.10-7.06 (m, 1H), 6.61 (s, 2H), 3.89 (t, J = 6.0 Hz, 2H), 3.63 (t, J = 8.0 Hz, 2H), 3.29 (t, J = 8.0 Hz, 2H), 2.95-2.88 (m, 1H), 2.35 (t, J = 6.0 Hz, 2H), 2.30 (s, 6H), 2.17-2.13, (m, 2H), 2.04-2.01 (m, 2H), 1.81-1.78 (m, 2H), 1.64-1.61 (m, 1H), 1.44-1.13 (m, 6H); >98% at 215 nm, MS (ESI) m/z = 560.2 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(cyclohexanesulfonamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (17). Prepared according to **GP2** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (22 mg, 0.062 mmol) and cyclohexanesulfonyl chloride (11 mg, 0.068

mmol). The title compound (16 mg, 0.026 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.28 (s, 1H), 8.86 (br s, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.40-7.33 (m, 2H), 7.16-7.12 (m, 1H), 6.73 (s, 2H), 3.89 (t, J = 6.0 Hz, 2H), 3.68-3.66 (m, 2H), 3.60-3.54 (m, 2H), 3.30 (t, J = 8.0 Hz, 2H), 2.85-2.77 (m, 1H), 2.33 (s, 6H), 2.26-2.20, (m, 2H), 2.010-2.00 (m, 5H), 1.85-1.82 (m, 2H), 1.69-1.66 (m, 1H); >98% at 215 nm, MS (ESI) m/z = 610.2 $(M+H)^+$.

General Procedure 3 (GP3): Linear Synthesis from phthalimide deprotection.

To a stirred solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (1.0 mmol) in CH_2Cl_2 (1.0 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.3 mmol), DMAP (2.1 mmol), Et_3N (3.2 mmol), and 2-(1,3-dioxoisoindolin-2-yl)ethane-1-sulfonamide (1.1 mmol) at ambient temperature. The reaction mixture was stirred for 15 h then concentrated *in vacuo*. The residue was dissolved in 1:1 mixture of CH_3CN/MeOH (1.0 mL) then filtered. The filtrate was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 95% CH_3CN 0.1% TFA) to yield 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((2-(1,3-dioxoisoindolin-2-yl)ethyl)sulfonyl)-1H-indole-2-carboxamide (0.70 mmol).

To a stirred slurry of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((2-(1,3-dioxoisoindolin-2-yl)ethyl)sulfonyl)-1H-indole-2-carboxamide (0.70 mmol) in MeOH (0.7 mL) was added hydrazine hydrate (0.77 mmol). The reaction mixture was stirred for 15 h at 50 °C then cooled to ambient temperature. The reaction was filtered and the white solid was washed with cold MeOH to give crude *N*-((2-aminoethyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide that was used in the subsequent reaction without further purification.

To a stirred solution of *N*-((2-aminoethyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (0.053 mmol) in CH_2Cl_2 (0.5 mL) was added TEA (0.16 mmol) followed by acyl chloride (0.065 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, warmed to ambient temperature and stirring for additional 15 h then concentrated *in vacuo*. The residue was dissolved in 1:1

mixture of CH_3CN/MeOH (1.0 mL) then filtered. The filtrate was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 95% CH_3CN 0.1% TFA)

***N*-((2-Acetamidoethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (18).** Prepared according to **GP3** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (20 mg, 0.054 mmol) and acetychloride (5.0 mg, 0.026 mmol). The title compound (5.2 mg, 0.010 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.57 (s, 1H), 9.01 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.52-7.37 (m, 2H), 7.21-7.16 (m, 2H), 6.76 (s, 2H), 5.93 (s, 1H), 3.88 (t, J = 4.0 Hz, 2H), 3.67-3.63 (m, 2H), 3.53-3.51 (m, 2H), 3.35 (t, 6.0 Hz, 1H), 2.33-2.26 (m, 8H), 1.92 (s, 3H); >98% at 215 nm, MS (ESI) m/z = 506.2 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(cyclohexanecarboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (19). Prepared according to **GP3** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (22 mg, 0.054 mmol) and cyclohexanecarbonylchloride (9.0 mg, 0.065 mmol). The title compound (11 mg, 0.018 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.58 (s, 1H), 9.16 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.16-7.13 (m, 2H), 6.74 (s, 2H), 5.95 (s, 1H), 3.88 (t, J = 6.0 Hz, 2H), 3.69-3.65 (m, 2H), 3.54-3.49 (m, 2H), 3.31 (t, J = 8.0 Hz, 2H), 2.36-2.22 (m, 8H), 2.03-1.95 (m, 1H), 1.80-1.73 (m, 4H), 1.42-1.04 (m, 10H); >98% at 215 nm, MS (ESI) m/z = 610.2 $(M+H)^+$.

6-Chloro-*N*-((2-(cyclohexanecarboxamido)ethyl)sulfonyl)- 3-(3-(naphthalen-1-yloxy)propyl)1*H*-indole-2-carboxamide (20). Prepared according to **GP3** from 6-chloro-3-(3-(naphthylen-1-yloxy)propyl)-1*H*-indole-2-carboxylic acid (21 mg, 0.054 mmol) and cyclohexanecarbonylchloride (9.0 mg, 0.065 mmol). The title compound (15 mg, 0.025 mg) was isolated as a white solid: >98% at 215 nm, MS (ESI) m/z = 596.2 $(M+H)^+$.

General Procedure 4 (GP4): Tandem Amide Coupling/Acylsulfonamide Formation.

To a stirred solution selected carboxylic acid (0.094 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.19 mmol), and HOBT

(0.020 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added 2-aminoethanesulfonamide hydrochloride (0.094 mmol). The reaction was stirred at 0 °C for 30 min, slowly warmed to ambient temperature and stirred for additional 15 h. To the reaction mixture, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 mmol), DMAP (0.19 mmol), and of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (0.094 mmol) were added then stirred for another 15 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in 1:1 mixture of CH_3CN/MeOH (1.0 mL) then filtered. The filtrate was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 95% CH_3CN 0.1% TFA).

***N*-((2-(1*H*-Indole-5-carboxamido)ethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (21).** Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 1*H*-indole-5-carboxylic acid (15 mg, 0.094 mmol). The title compound (22 mg, 0.036 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.76 (br s, 1H), 9.15 (br s, 1H), 8.25 (br s, 1H), 7.97 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.33 (m, 2H), 7.41 (m, 2H), 7.14 (t, J = 8.0 Hz, 1H), 6.76 (t, J = 8.0 Hz, 1H), 6.72 (s, 2H), 6.48 (m, 1H), 3.94 (m, 2H), 3.85 (t, J = 8.0 Hz, 2H), 3.72 (m, 2H), 3.30 (t, J = 8.0 Hz, 2H), 2.26 (s, 6H), 2.21 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 607.2 $(M+H)^+$.

***N*-((2-(1*H*-Indole-6-carboxamido)ethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (22).** Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 1*H*-indole-6-carboxylic acid (15 mg, 0.094 mmol). The title compound (18 mg, 0.030 mmol)was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.92 (s, 1H), 8.37 (s, 1H), 7.6 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 4.0 Hz, 1H), 7.265 (d, J = 4.0 Hz, 2H), 7.22-7.02 (m, 5H), 7.58 (s, 2H), 6.38 (s, 1H), 3.90 (br s, 2H), 3.79 (br s, 2H), 3.71 (t, J = 6.0 Hz, 2H), 3.15-3.09 (m, 2H), 2.26 (s, 6H), 2.01-1.98 (m, 3H); >98% at 215 nm, MS (ESI) m/z = 607.2 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(1-methyl-1*H*-indole-3-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (23). Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33

mg, 0.094 mmol) and 1-methyl-1*H*-indole-3-carboxylic acid (17 mg, 0.094 mmol). The title compound (38 mg, 0.061 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.10 (d, J = 8.0 Hz, 1H), 8.02 (m, 1H), 7.57 (d, J = 4.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.29 (m, 1H), 7.16 (m, 1H), 7.10-7.04 (m, 2H), 6.70 (s, 2H), 3.81-3.73 (m, 6H), 3.44 (s, 4H), 2.95 (m, 2H), 2.25 (s, 7H), 1.83 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 621.2 $(M+H)^+$.

***N*-((2-(2-(1*H*-Indol-3-yl)acetamido)ethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (24).** Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 2-(1*H*-indol-3-yl)acetic acid (17 mg, 0.094 mmol). The title compound (15 mg, 0.016 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.81 (s, 1H), 8.18 (br s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.41-7.29 (m, 5H), 7.17-7.06 (m, 5H), 6.99 (s, 1H), 6.64 (s, 3H), 6.61 (s, 1H), 6.41 (br s, 1H), 3.95 (t, J = 6.0 Hz, 2H), 3.84 (t, J = 6.0 Hz, 2H), 3.70-3.64 (m, 5H), 3.55 (s, 3H), 3.35-3.25 (m, 5H), 2.30 (d, J = 8.0 Hz, 14H), 2.22-2.17 (m, 5H), 2.01 (s, 2H); >98% at 215 nm, MS (ESI) m/z = 621.1 $(M+H)^+$.

***N*-((2-(Benzofuran-2-carboxamido)ethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (25).** Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and benzofuran-2-carboxylic acid (15 mg, 0.094 mmol). The title compound (22 mg, 0.036 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.35-7.22 (m, 7H), 7.15-7.11 (m, 2H), 6.74 (s, 2H), 3.93-3.86 (m, 5H), 3.74-3.71 (m, 2H), 3.29 (t, J = 6.0 Hz, 2H), 2.35-2.20 (m, 11H); >98% at 215 nm, MS (ESI) m/z = 608.1 $(M+H)^+$.

(*S*)-3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(indoline-2-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (26). Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and (*S*)-indoline-2-carboxylic acid (15 mg, 0.094 mmol). The title compound (20 mg, 0.033 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.25 (s, 1H), 9.17 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.35-7.00 (m, 6H), 6.81-6.64 (m, 4H), 3.92-3.82 (m, 4H), 3.69 (d, J = 8.0 Hz, 2H),

3.27 (t, J = 6.0 Hz, 2H), 2.34-2.18 (m, 9H); >98% at 215 nm, MS (ESI) m/z = 609.1 $(M+H)^+$.

(*S*)-6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(indoline-2-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (27). Prepared according to **GP4** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and (*S*)-indoline-2-carboxylic acid 1 (15 mg, 0.094 mmol). The title compound (25 mg, 0.039 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, MeOD): δ (ppm) 7.41 (d, J = 8.0 Hz, 1H), 7.365 (d, J = 4.0 Hz, 1H), 7.33-7.30 (m, 2H), 7.19-7.15 (m, 1H), 7.01-6.94 (m, 2H), 6.77 (s, 1H), 6.63 (s, 2H), 3.96-3.92 (m, 5H), 3.81 (t, J = 6.0 Hz, 2H), 3.09 (t, J = 8.0 Hz, 2H), 2.35-2.30 (m, 8H), 1.99 (t, J = 6.0 Hz, 2H); >98% at 215 nm, MS (ESI) m/z = 643.1 $(M+H)^+$.

(*R*)-6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(indoline-2-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (28). Prepared according to **GP4** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and (*R*)-indoline-2-carboxylic acid (15 mg, 0.094 mmol). The title compound (15 mg, 0.023 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.65 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.56-7.50 (m, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.15 (t, J = 8.0 Hz, 1H), 7.05-6.96 (m, 2H), 6.88 (s, 1H), 6.74-6.68 (m, 2H), 3.85-3.76 (m, 8H), 3.06 (d, J = 8.0 Hz, 2H), 2.26 (t, J = 6.0 Hz, 9H), 1.93 (t, J = 6.0 Hz, 2H); >98% at 215 nm, MS (ESI) m/z = 643.0 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(1-phenyl-1*H*-pyrrole-2-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (29). Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 1-phenyl-1*H*-pyrrole-2-carboxylic acid (18 mg, 0.094 mmol). The title compound (31 mg, 0.049 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 633.2 $(M+H)^+$.

***N*-((2-(1-Benzyl-1*H*-pyrrole-2-carboxamido)ethyl)sulfonyl)-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (30).** Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 1-benzyl-1*H*-pyrrole-2-carboxylic acid (19 mg, 0.094 mmol). The title compound (29 mg, 0.045 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz,

MeOD): δ (ppm) 9.55 (br s, 1H), 8.94 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.39-7.07 (m, 5H), 7.06 (d, J = 8.0 Hz, 2H), 6.76-6.73 (m, 3H), 6.49-6.40 (m, 2H), 6.07 (t, J = 4.0 Hz, 1H), 3.85 (t, J = 4.0 Hz, 2H), 3.77-3.72 (m, 2H), 3.59-3.56 (m, 2H), 3.29 (t, J = 6.0 Hz, 2H), 2.32-2.21 (m, 8H); >98% at 215 nm, MS (ESI) m/z = 647.2 $(M+H)^+$.

***N*-((2-(1*H*-Pyrrole-2-carboxamido)ethyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (31).** Prepared according to **GP4** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and 1-(*tert*-butoxycarbonyl)-1*H*-pyrrole-2-carboxylic acid (20 mg, 0.094 mmol). The title compound (22 mg, 0.039 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.12 (br s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.455 (d, J = 4.0 Hz, 1H), 7.04-6.99 (m, 3H), 6.75 (s, 2H), 3.92 (t, J = 6Hz, 2H), 3.70-3.67 (m, 2H), 3.32 (s, 15H), 3.27 (t, J = 8.0 Hz, 2H), 3.13 (t, J = 8.0 Hz, 2H), 2.27 (s, 6H), 2.01 (t, J = 6.0 Hz, 2H); >98% at 215 nm, MS (ESI) m/z = 591.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(1-methyl-1*H*-pyrrole-2-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (32). Prepared according to **GP4** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 1-methyl-1*H*-pyrrole-2-carboxylic acid (12 mg, 0.094 mmol). The title compound (29 mg, 0.050 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.11 (t, J = 4.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 2H), 6.81 (m, 1H), 6.73 (s, 2H), 6.61 (m, 1H), 3.89 (t, J = 8.0 Hz, 2H), 3.75 (m, 2H), 3.74 (s, 3H), 3.63 (m, 2H), 3.13 (t, J = 8.0 Hz, 2H), 2.25 (s, 6H), 1.98 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 571.2 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(furan-2-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (33). Prepared according to G**P4** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and furan-2-carboxylic acid (0.094 mmol). The title compound (30 mg, 0.051 mmol)was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 592.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(furan-3-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (34). Prepared according to

GP4 from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and furan-3-carboxylic acid (10 mg, 0.094 mmol). The title compound (25 mg, 0.021 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 592.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (35). Prepared according to **GP4** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and 3-(2-hydroxyphenyl)-1*H*-pyrazole-5-carboxylic acid hydrate (21 mg, 0.094 mmol). The title compound (15 mg, 0.022 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.30 (br s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.50 (s, 3H), 7.355 (d, J = 4.0 Hz, 1H), 6.81 (m, 1H), 7.11 (d, J = 8.0 Hz, 2H), 6.90-6.86 (m, 3H), 6.65 (s, 2H), 3.88 (t, J = 4.0 Hz, 2H), 3.74 (s, 3H), 3.59-3.54 (m, 2H), 3.35 (s, 5H), 3.22-3.13 (m, 4H), 2.22 (s, 6H), 2.00 (t, J = 8.0 Hz, 2H); >98% at 215 nm, MS (ESI) m/z = 684.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(2-fluorobenzamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (36). Prepared according to **GP2** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 2-fluorobenzoyl chloride (15 mg, 0.094 mmol). The title compound (28 mg, 0.048 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.64 (br s, 1H), 9.06 (br s, 1H), 7.97 (dt, J = 8.0, 1.2 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.39 (m, 3H), 7.16 (m, 2H), 7.00 (dd, J = 12.0, 8.0 Hz, 1H), 6.73 (s, 2H), 3.91 (m, 2H), 3.85 (t, J = 8.0 Hz, 2H), 3.72 (m, 2H), 3.31 (t, J = 8.0 Hz, 2H), 2.27 (s, 6H), 2.25 (m, 2H). >98% at 215 nm, MS (ESI) m/z = 586.2 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-fluorobenzamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (37). Prepared according to **GP2** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 3-fluorobenzoyl chloride (15 mg, 0.094 mmol). The title compound (30 mg, 0.051 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 586.2 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-N-((2-(4-

fluorobenzamido)ethyl)sulfonyl)-1H-indole-2-carboxamide (38). Prepared according to **GP2** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.094 mmol) and 4-fluorobenzoyl chloride (15 mg, 0.094 mmol). The title compound (22 mg, 0.037 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 586.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(2-(trifluoromethyl)benzamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (39). Prepared according to **GP2** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and 2-(trifluoromethyl)benzoyl chloride (19 mg, 0.094 mmol). The title compound (27 mg, 0.040 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 670.0 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-(trifluoromethyl)benzamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (40). Prepared according to **GP2** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and 3-(trifluoromethyl)benzoyl chloride (19 mg, 0.094 mmol). The title compound (20 mg, 0.025 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.92 (s, 1H), 8.05 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.615 (d, J = 8.0 Hz, 3H), 7.52-7.48 (m, 2H), 7.07-7.04 (dd, J = 12.0, 8.0 Hz, 1H), 6.72 (s, 2H), 3.87 (br s, 5H), 3.775 (d, J = 4.0 Hz, 3H), 3.04 (s, 2H), 2.26 (s, 7H), 1.93 (s, 2H), 2.25 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 670.0 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(4-(trifluoromethyl)benzamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (41). Prepared according to **GP2** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (37 mg, 0.094 mmol) and 4-(trifluoromethyl)benzoyl chloride (19 mg, 0.094 mmol). The title compound (28 mg, 0.042 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 670.0 $(M+H)^+$.

***N*-((2-Acetamidoethyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxamide (42).** Prepared according to **GP3** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (21 mg, 0.054 mmol) and acetylchloride (5.0 mg, 0.065 mmol). The title compound

(11 mg, 0.020 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.05 (s, 1H), 7.695 (d, J = 4.0 Hz, 1H), 7.53 (s, 1H), 7.08-7.05 (m, 1H), 6.74 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.63 (br s, 2H), 3.50-3.46 (m, 3H), 3.22-3.15 (m, 2H), 2.27 (s, 6H), 2.02 (t, J = 8.0 Hz, 2H), 1.71 (s, 3H); >98% at 215 nm, MS (ESI) m/z = 540.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(2,2,2-trifluoroacetamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (43). Prepared according to **GP3** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (21 mg, 0.054 mmol) and 2,2,2-trifluoroacetic anhydride (14 mg, 0.065 mmol). The title compound (12 mg, 0.020 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.63 (t, J = 6.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.535 (d, J = 4.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.74 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.78 (br s, 2H), 3.68-3.63 (m, 2H), 3.17 (t, J = 8.0 Hz, 2H), 2.27 (s, 6H), 2.02 (t, J = 8.0 Hz, 2H); >98% at 215 nm, MS (ESI) m/z = 594.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-propionamidoethyl)sulfonyl)-1*H*-indole-2-carboxamide (44). Prepared according to **GP3** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (21 mg, 0.054 mmol) and propionyl chloride (6.0 mg, 0.065 mmol). The title compound (14 mg, 0.025 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.95 (br s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 6.74 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.66 (br s, 2H), 3.51-3.47 (m, 2H), 3.17 (t, J = 6.0 Hz, 2H), 2.27 (s, 6H), 2.04-1.96 (m, 4H); >98% at 215 nm, MS (ESI) m/z = 554.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-isobutyramidoethyl)sulfonyl)-1*H*-indole-2-carboxamide (45). Prepared according to **GP3** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (21 mg, 0.054 mmol) and isobutyryl chloride (6.5 mg, 0.065 mmol). The title compound (12 mg, 0.021 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.94 (t, J = 6.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.075 (dd, J = 12.0 Hz, 1H), 6.74 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.5 (br s, 2H), 3.52-3.47 (m, 2H), 3.17 (t, J = 6.0 Hz, 2H), 2.29-2.22 (m, 7H), 2.04 (t, J = 8.0 Hz, 2H), .93 (d, J = 8.0

Hz, 6H); >98% at 215 nm, MS (ESI) m/z = 568.2 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(2-ethylbutanamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (46). Prepared according to **GP3** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (21 mg, 0.054 mmol) and 2-ethylbutanoyl chloride (8.8 mg, 0.065 mmol). The title compound (16 mg, 0.027 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.05 (t, J = 6.0 Hz, 1H), 7.70 (d, J = 12.0 Hz, 1H), 7.53 (s, 1H), 7.08 (dd, J = 12.0 Hz, 1H), 6.74 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.66 (t, J = 8.0 Hz, 2H), 3.54-3.50 (m, 2H), 3.17 (t, J = 6.0 Hz, 2H), 2.27 (s, 6H), 2.05-2.00 (m, 2H), 1.90-1.86 (m, 1H), 1.44-1.27 (m, 4H), 0.74 (t, J = 6.0 Hz, 6H); >98% at 215 nm, MS (ESI) m/z = 596.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((2-(3-methylbutanamido)ethyl)sulfonyl)-1*H*-indole-2-carboxamide (47). Prepared according to **GP3** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (21 mg, 0.054 mmol) and isovaleryl chloride (8.2 mg, 0.065 mmol). The title compound (10 mg, 0.017 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) m/z = 582.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-(phenylsulfonyl)-1*H*-indole-2-carboxamide (49). Prepared according to **GP1** from 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (33 mg, 0.097 mmol) and benzenesulfonamide (17 mg, 0.11 mmol). The title compound (35 mg, 0.071 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.73 (br s, 1H), 8.94 (br s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.40-7.32 (m, 4H), 7.16 (t, J = 8.0 Hz, 1H), 6.76 (s, 2H), 3.85 (t, J = 8.0 Hz, 2H), 3.36 (t, J = 8.0 Hz, 2H), 2.33 (s, 6H), 2.32-2.27 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 497.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-(phenylsulfonyl)-1*H*-indole-2-carboxamide (50). Prepared according to **GP1** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (38 mg, 0.097 mmol) and benzenesulfonamide (17 mg, 0.11 mmol). The title compound (40 mg, 0.075 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.04 (d, J = 8.0 Hz,

2H), 7.70 (m, 1H), 7.64 (m, 3H), 7.48 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.71 (s, 2H), 3.84 (t, *J* = 8.0 Hz, 2H), 3.06 (t, *J* = 8.0 Hz, 2H), 2.27 (s, 6H), 1.91 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 531.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-N-(pyridin-4-ylsulfonyl)-1H-indole-2-carboxamide (51). Prepared according to **GP1** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (33 mg, 0.097 mmol) and pyridine-4-sulfonamide (17 mg, 0.11 mmol). The title compound (27 mg, 0.054 mmol) was isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.88 (m, 2H), 7.95 (m, 2H), 7.60 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.24 (m, 1H), 7.01 (m, 1H), 6.72 (s, 2H), 3.87 (t, *J* = 8.0 Hz, 2H), 3.11 (m, 2H), 2.26 (s, 6H), 1.95 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 498.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-(furan-2-ylsulfonyl)-1H-indole-2-carboxamide (52). Prepared according to **GP1** from 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid **1** (38 mg, 0.097 mmol) and furan-2-sulfonamide (16 mg, 0.11 mmol). The title compound (32 mg, 0.062 mmol) was isolated as a white solid. >98% at 215 nm, MS (ESI) *m/z* = 521.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-*N*-(phenylsulfonyl)-7-(pyridin-3-yl)-1*H*-indole-2-carboxamide (53) General Procedure 5 (GP5). A solution of ethyl 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate (50 mg, 0.11 mmol), pyridin-3-ylboronic acid (14.6 mg, 0.12 mmol), $Pd(PPh_3)$ (6.3 mg, 5.4 μmol) and CsF (49.0 mg, 0.32 mmol) in ethanol (0.18 mL) and DME (0.35 mL) was purged under Ar for 10 min. The mixture was then heated to 120 °C in Biotage Initiator for 25 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (Combi-flash Rf Hexane/EtOAc gradient 10–60%) to give ethyl 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(pyridin-3-yl)-1H-indole-2-carboxylate (45 mg, 0.10 mmol) as a yellow oil. >98% at 215 nm, MS (ESI) *m/z* = 463.2 $(M+H)^+$.

A solution of ethyl 3-(3-(4-chloro-3, 5-dimethylphenoxy)propyl)-7-(pyridin-3-yl)-1H-indole-2-carboxylate (45 mg, 0.10 mmol) and LiOH (0.24 mL, 2 N, 0.48 mmol) in EtOH (0.38 mL) and THF (0.10 mL) was heated to 40 °C. After 16 h, a solution of HCl (0.1 mL, 6 N, 0.6 mmol) was added to acidify the reaction mixture. The solvent was removed under reduced pressure and H_2O (3 mL) was added. The resulting suspension

was filtered, and solid washed with H_2O (5.0 mL x 3) to give 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(pyridin-3-yl)-1H-indole-2-carboxylic acid (30 mg, 0.07 mmol) as a white solid. >98% at 215 nm, MS (ESI) *m/z* = 435.1 $(M+H)^+$.

A solution of 3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(pyridin-3-yl)-1H-indole-2-carboxylic acid (13.0 mg, 0.030 mmol), benzensulfonamide (5.2 mg, 0.033 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.6 mg, 0.05 mmol) and DMAP (7.30 mg, 0.060 mmol) in CH_2Cl_2 (0.60 mL) was stirred at ambient temperature for 16 h. The reaction mixture was concentrated down, and the crude product was purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 30-70% CH_3CN 0.1% TFA) to give the title compound (9.2 mg, 0.016 mmol) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 11.03 (s, 1H, NH), 9.30 (s, 1H), 8.89 (d, *J* = 5.3 Hz, 1H), 8.50 (d, *J* = 8.2 Hz, 1H), 8.01 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.55 (dd, 7.5, 7.5 Hz, 1H), 7.44 (dd, *J* = 7.8, 7.5 Hz, 2H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.24 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.63 (s, 2H), 3.89 (t, *J* = 6.1 Hz, 2H), 3.30 (t, *J* = 7.1 Hz, 2H), 2.32 (s, 6H), 2.17-2.13 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 574.2 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-7-(4-methylpyridin-3-yl)-*N*-(phenylsulfonyl)-1*H*-indole-2-carboxamide (54). The title compound was prepared as a white solid according to **GP5** by substituting pyridin-3-ylboronic acid with (4-methylpyridin-3-yl)boronic acid in 17% overall yield. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.71 (s, 1H, NH), 8.76 (s, 1H), 8.68 (d, *J* = 5.3 Hz, 1H), 7.97 (d, *J* = 7.4 Hz, 2H), 7.86 (d, *J* = 5.4 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.45 (dd, 7.9, 7.5 Hz, 2H), 7.24-7.18 (m, 2H), 6.65 (s, 2H), 3.93 (t, *J* = 6.0 Hz, 2H), 3.31 (t, *J* = 7.3 Hz, 2H), 2.52 (s, 3H), 2.33 (s, 6H), 2.18-2.14 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 588.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-7-(2-methylpyridin-3-yl)-N-(phenylsulfonyl)-1H-indole-2-carboxamide (55). The title compound was prepared as a white solid according to **GP5** by substituting pyridin-3-ylboronic acid with (2-methylpyridin-3-yl)boronic acid in 30% overall yield. ^{1}H NMR (400MHz, $CDCl_3$): δ 10.65 (s, 1H, NH), 8.69 (d, *J* = 5.3 Hz, 1H), 8.18 (d, *J* = 6.4 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.74 (dd, *J* = 6.2, 6.2 Hz, 1H), 7.56 (dd, *J* = 7.5, 7.1 Hz,

1H), 7.45 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.25-7.19 (m, 2H), 6.64 (s, 2H), 3.91 (t, *J* = 6.1 Hz, 2H), 3.32 (t, *J* = 6.2 Hz, 2H), 2.73 (s, 3H), 2.32 (s, 6H), 2.18-2.14 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 588.1 $(M+H)^+$.

3-(3-(4-Chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-*N*-(phenylsulfonyl)-1*H*-indole-2-carboxamide (56). The title compound was prepared as a white solid according to **GP5** by substituting pyridin-3-ylboronic acid with 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole in 41% overall yield. ^{1}H NMR (400MHz, $CDCl_3$): 8.90 (s, 1H), 8.34 (d, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 6.9 Hz, 1H), 6.67 (s, 2H), 6.65 (s, 1H), 3.92 (t, *J* = 5.7 Hz, 2H), 3.36 (t, *J* = 7.1 Hz, 2H), 3.15 (s, 3H), 2.63 (s, 3H), 2.34 (s, 6H), 2.23 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 591.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(2-methylpyridin-3-yl)-N-(phenylsulfonyl)-1H-indole-2-carboxamide (57). The title compound was prepared as a white solid according to **GP5** by substituting 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate and pyridin-3-ylboronic acid with ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate and (2-methylpyridin-3-yl)boronic acid in 23% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.94 (s, 1H, NH), 8.77 (d, *J* = 4.3 Hz, 1H), 7.99 (m, 3H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.72-7.67 (m, 2H), 7.64-7.60 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.72 (s, 2H), 3.88 (t, *J* = 6.4 Hz, 2H), 3.10 (t, *J* = 6.6 Hz, 2H), 2.27(s, 9H), 1.96-1.89 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 622.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1*H*-pyrazol-4-yl)-*N*-(phenylsulfonyl)-1*H*-indole-2-carboxamide (58). The title compound was prepared as a white solid according to **GP5** by substituting 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate and pyridin-3-ylboronic acid with ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate and (3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol in 39% overall yield. >98% at 215 nm, MS (ESI) *m/z* = 625.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-(phenylsulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (59). The title compound

was prepared as a white solid according to **GP5** by substituting 7-bromo-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate and pyridin-3-ylboronic acid with ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1H-indole-2-carboxylate and 1,3,5-trimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in 35% overall yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.81 (s, 1H, NH), 8.02-7.99 (comp, 2H), 7.72 (dd, *J* = 7.7, 7.1 Hz, 1H), 7.66-7.61 (comp, 3H), 7.20 (d, *J* = 8.5 Hz 1H), 6.70 (s, 2H), 3.88 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 3.10 (t, *J* = 6.3 Hz, 2H), 2.26(s, 6H), 2.01 (s, 3H), 1.93 (s, 3H), 1.92-1.88 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 639.1 $(M+H)^+$.

5-(*N*-(6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid (60). A solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxylic acid (49 mg, 0.10 mmol), methyl 5-sulfamoylfuran-2-carboxylate (23 mg, 0.11 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (23 mg, 0.12 mmol) and DMAP (24 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) was stirred 16 h at ambient temperature. The reaction mixture was concentrated, and the residue was purified reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient 40-90% CH_3CN 0.1% TFA) to give methyl 5-(N-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-indole-2-carbonyl)sulfamoyl)furan-2-carboxylate (23 mg, 0.034 mmol). >98% at 215 nm, MS (ESI) *m/z* = 673.1 $(M+H)^+$.

A solution of methyl 5-(N-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carbonyl)sulfamoyl)furan-2-carboxylate (23 mg, 0.034 mmol) in EtOH (0.40 mL), THF (0.10 mL) and LiOH (0.075 mL, 2 N, 0.15 mmol) was stirred at 40 °C for 15 h. The reaction was quenched by addition of aq. HCl (0.02 mL, 6 N, 0.12 mmol), and the mixture was concentrated. The residue was washed with H_2O (1.0 mL x 3) to give the title compound (15 mg, 0.023 mmol) as white solid. >98% at 215 nm, MS (ESI) *m/z* = 659.1 $(M+H)^+$.

5-(*N*-(6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid

(61). The title compound was prepared as a white solid according to procedures described for preparing compound (**60**) by substituting 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(3,5-dimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxylic acid with 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxylic acid in 56% overall yield. 1H NMR (400 MHz, DMSO-d_6): δ 10.62 (s, 1H, NH), 7.67 (d, J = 8.8 Hz, 1H), 7.43 (brs, 1H), 7.35 (d, J = 3.5 Hz 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.73 (s, 2H), 3.92 (t, J = 6.4 Hz, 2H), 3.80 (s, 3H), 3.15 (t, J = 7.3 Hz, 2H), 2.27(s, 6H), 2.02 (s, 3H), 1.94 (s, 3H), 1.98-1.93 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 673.1 $(M+H)^+$.

Mixture of 4- and 5-(*N*-(7-(1-(2-((6-(3-carboxy-4-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)benzamido)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid (62). A solution of ethyl 7-bromo-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (**76b**, 245 mg, 0.49 mmol) and *tert*-butyl 2-(3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)acetate (**78**, 150 mg, 0.45 mmol) in aq. K_2CO_3 (2N, 1.5 mL, 3.0 mmol) and 1,4-dioxane (0.75 mL) was purged under Ar for 10 min. $Pd(PPh_3)$ (2.6 mg, 0.022 mmol) was added to the reaction mixture which was heated to 115 °C in Biotage Initiator for 1h. Upon cooling to ambient temperature, the reaction mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Hexanes/EtOAc gradient to 50% EtOAc) to yield ethyl 7-(1-(2-(*tert*-butoxy)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate as a white solid (195 mg, 0.31 mmol). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.68 (s), 7.69 (d, J = 8Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.76 (s, 2H), 5.76 (s, 1H), 4.94-4.82 (m, 2H), 4.31-4.26 (m, 2H), 4.01-3.93 (t, J = 6.0 Hz, 2H), 3.93 (s, 1H), 3.20-3.16 (t, J = 8.0 Hz, 2H), 2.28 (s, 6H), 2.06-2.02 (m, 2H), 1.93-1.91 (m, 6H), 1.45 (s, 9H), 1.32-1.29 (t, J =6.0 Hz, 3H); >98% at 215 nm, MS (ESI) *m/z* = 628.1 $(M+H)^+$.

To a stirred solution of ethyl 7-(1-(2-(*tert*-butoxy)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-

carboxylate (106 mg, 0.169 mmol) in CH_2Cl_2 (1.0 mL) at ambient temperature was added TFA (0.5 mL) then stirred for 2 h. Upon completion, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ aq. solution. The organic layer was separated and concentrated in vacuo to give crude 2-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(ethoxycarbonyl)-1*H*-indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)acetic acid (**79**) which was used without further purification in the next step. MS (ESI) m/z = 572.1 $(M+H)^+$.

To a stirred solution of 2-(4-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-2-(ethoxycarbonyl)-1*H*-indol-7-yl)-3,5-dimethyl-1*H*-pyrazol-1-yl)acetic acid (**79**, 62 mg, 0.11 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (31 mg, 0.16 mmol), Et_3N (110 mg, 1.1 mmol) and HOBT (1.5 mg, 0.011 mmol) in CH_2Cl_2 (0.5 mL) at ambient temperature was added *tert*-butyl (6-aminohexyl)carbamate (26 mg, 0.120 mmol). The reaction was stirred for 15 h then concentrated. The residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH gradient to 5% MeOH) to yield ethyl 7-(1-(2-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (**80**, 66 mg, 0.087 mmol) as a white solid. MS (ESI) m/z = 770.1 $(M+H)^+$.

To a stirred solution of ethyl 7-(1-(2-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylate (**80**, 69 mg, 0.090 mmol) in THF (0.9 mL) was added aq. LiOH (2M, 0.7 mL) then stirred for 15h at ambient temperature. The reaction was acidified with aq. HCl (3M) to pH=13 and extracted with ethyl acetate (3 x 3 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by silica gel flash chromatography (CH_2Cl_2/MeOH gradient to 15% MeOH) to yield 7-(1-(2-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (46 mg, 0.061 mmol) as a white foam. MS (ESI) m/z = 742.1 $(M+H)^+$.

To a stirred solution of 7-(1-(2-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-

dimethylphenoxy)propyl)-1*H*-indole-2-carboxylic acid (72 mg, 0.097 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (37 mg, 0.194 mmol), and DMAP (36 mg, 0.291 mmol) in CH_2Cl_2 (0.5 mL) at ambient temperature was added ethyl 5-sulfamoylfuran-2-carboxylate (27 mg, 0.12 mmol) then stirred for additional 15 h. The reaction mixture was adsorbed onto silica gel and purified by silica gel flash chromatography (CH_2Cl_2/MeOH gradient to 10% MeOH) to yield ethyl 5-(*N*-(7-(1-(2-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylate (**81**, 89 mg, 0.094 mmol) as a white solid. MS (ESI) m/z = 943.3 $(M+H)^+$.

To a stirred solution of ethyl 5-(*N*-(7-(1-(2-((6-((*tert*-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylate (**81**, 87 mg, 0.092 mmol) in THF (1.0 mL) was added aq. LiOH (2M, 0.8 mL). The reaction was stirred at 35 °C for 15 h then acidified with aq. HCl (3M) to pH=13 and extracted with ethyl acetate (3 x 3 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield crude 5-(*N*-(7-(1-(2-((6-((tert-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid, which was used in the next step without further purification. MS (ESI) m/z = 915.3 $(M+H)^+$.

To a solution of crude 5-(*N*-(7-(1-(2-((6-((tert-butoxycarbonyl)amino)hexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid (0.092 mmol) in CH_2Cl_2 (1.0 mL) was added TFA (0.3 mL) and stirred for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in 1:1 mixture of CH_3CN/MeOH (1.0 mL) then filtered. The filtrate was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 50-95% CH_3CN 0.1% TFA) to give 5-(*N*-(7-(1-(2-((6-aminohexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-

indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid (**82**, 42 mg, 0.052 mmol). >98% at 215 nm, MS (ESI) *m/z* = 815.2 $(M+H)^+$.

A solution of 5-(*N*-(7-(1-(2-((6-aminohexyl)amino)-2-oxoethyl)-3,5-dimethyl-1*H*-pyrazol-4-yl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid (**82**, 51 mg, 0.055 mmol) and Et(*i*-Pr)$_2$N (85 mg, 0.66 mmol) in a mixture of CH_2Cl_2 (0.4 mL) and DMF (0.1 mL) was added to a vial charged with an isomeric mixture of 4- and 5-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)-2-(6-hydroxy-3-oxo-3*H*-xanthen-9-yl)benzoic acid (23 mg, 0.049 mmol). The reaction mixture was stirred for 2h at ambient temperature then concentrated *in vacuo*. The residue was purified by reverse phase preparatory HPLC (H_2O/CH_3CN gradient to 55-95% CH_3CN in 0.1% TFA) to give the title compound **62** as a yellow/orange solid (15 mg, 0.013 mmol). MS (ESI) *m/z* = 587.1 $(M/2+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((3-((3-(trifluoromethyl)benzamido)methyl)phenyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (64). To a solution of 3-(aminomethyl)benzenesulfonamide hydrochloride (40 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was added Et(*i*-Pr)$_2$N (100 mg, 0.78 mmol), and the reaction was cooled to -78 °C. A solution of 3-(trifluoromethyl)benzoyl chloride (35 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 5 minutes, the reaction was quenched with MeOH (0.5 mL) and concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 15-70% CH_3CN, 0.1% TFA.) to afford *N*-(3-sulfamoylbenzyl)-3-(trifluoromethyl)benzamide trifluoroacetic acid salt (11 mg, 0.030 mmol).

To a solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (15 mg, 0.030 mmol) and HATU (12 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) was added Et(*i*-Pr)$_2$N (50 mg, 0.38 mmol), and the reaction was stirred for 20 min at ambient temperature. A solution of *N*-(3-sulfamoylbenzyl)-3-(trifluoromethyl)benzamide trifluoroacetic acid salt (11 mg, 0.030 mmol) and Et(*i*-Pr)$_2$N (50 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) was added, and the reaction was stirred for additional 48 h. The mixture was diluted with CH_2Cl_2 (15 mL)/H_2O (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2

(2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 35-95% CH_3CN, 0.1% TFA.) to afford the title compound (3 mg, 0.0036 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.79 (s, 1H), 9.44 (s, 1H), 8.23 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.96 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.73-7.60 (m, 4H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.70 (s, 2H), 4.61 (d, *J* = 5.8 Hz, 2H), 3.87 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.64 (s, 6H), 2.00 (s, 3H), 1.92 (s, 3H), 1.90-1.86 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 840.1 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((3-((2-(trifluoromethyl)benzamido)methyl)phenyl)sulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (63). The title compound was prepared (4 mg, 0.0059 mmol) as a colorless oil following the same procedure as described for compound **64** using 2-(trifluoromethyl)benzoyl chloride (38 mg, 0.18 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): 10.80 (s, 1H), 9.14 (t, *J* = 6.0 Hz, 1H), 7.96 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.67-7.58 (m, 5H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.68 (s, 2H), 4.54 (d, *J* = 6.0 Hz), 3.87 (t, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 3.11 (t, *J* = 8.0 Hz, 2H), 2.26 (s, 6H), 2.01 (s, 3H), 1.94-1.90 (m, 5H); >98% at 215 nm, MS (ESI) *m/z* = 840.1 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((3-((1-methyl-1H-pyrrole-2-carboxamido)methyl)phenyl)sulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (65). To a solution of 1-methyl-1*H*-pyrrole-2-carboxylic acid (23 mg, 0.18 mmol), HATU (70 mg, 0.18 mmol) in DMF (2 mL) was added $Et(i\text{-}Pr)_2N$ (100 mg, 0.78 mmol), and the reaction was stirred at ambient temperature for 20 min. 3-(Aminomethyl)benzenesulfonamide hydrochloride (40 mg, 0.18 mmol) was added, and the reaction was stirred for additional 3 h. The reaction was diluted with CH_2Cl_2 (15 mL)/H_2O (15 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 15-70% CH_3CN, 0.1% TFA.) to afford 1-methyl-*N*-(3-sulfamoylbenzyl)-1H-pyrrole-2-carboxamide trifluoroacetic acid salt (7 mg, 0.017 mmol).

The title compound was prepared (4 mg, 0.0052 mmol) as a colorless oil following the same procedure as described for compound **64** using 1-methyl-*N*-(3-sulfamoylbenzyl)-1H-pyrrole-2-carboxamide trifluoroacetic acid salt (7 mg, 0.017 mmol). ^{1}H NMR (500 MHz, DMSO-d_6): 10.80 (s, 1H), 8.65 (t, *J* = 6.0 Hz, 1H), 7.91 (s, 1H), 7.90 (s, 1H), 7.66-7.57 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 1H), 6.90 (t, *J* = 2.0 Hz, 1H), 6.82 (dd, *J* = 1.6, 3.8 Hz, 1H), 6.72 (s, 2H), 6.01 (dd, *J* = 2.6, 3.8 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.89 (t, *J* = 6.2 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.10 (t, *J* = 6.8 Hz, 2H), 2.27 (s, 6H), 2.01 (s, 3H), 1.93 (s, 3H), 1.92-1.89 (m, 2H); >98% at 215 nm, MS (ESI) *m*/*z* = 775.1 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((3-((furan-3-carboxamido)methyl)phenyl)sulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (66). The title compound was prepared (2 mg, 0.0026 mmol) as a colorless oil following the same procedure as described for compound **64** using furan-3-carbonyl chloride (25 mg, 0.19 mmol). ^{1}H NMR (400 MHz, DMSO-d_6): 10.78 (s, 1H), 8.83 (s, 1H), 8.18 (s, 1H), 7.87 (s, 2H), 7.70 (s, 1H), 7.61-7.54 (m, 3H), 7.16 (d, *J* = 15.0 Hz, 1H), 6.84 (s, 1H), 6.70 (s, 2H), 4.49 (s, 2H), 3.87 (t, *J* = 6.0 Hz, 2H), 3.75 (s, 3H), 3.16-3.14 (m, 2H), 2.24 (s, 6H), 1.99 (s, 3H), 1.91-1.88 (m, 5H); >98% at 215 nm, MS (ESI) *m*/*z* = 762.1 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((3-(isobutyramidomethyl)phenyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (68). To a solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (40 mg, 0.080 mmol) in DMF (1.5 mL) were added 3-cyanobenzenesulfonamide (32 mg, 0.18 mmol), HBTU (61 mg, 0.16 mmol), Et_3N (23 µL, 0.16 mmol), and the mixture was stirred at ambient temperature for 48 h. The reaction mixture was extracted with CH_2Cl_2 (3x15 mL), dried over Na_2SO_4 then concentrated *in vacuo*. The residue was dissolved in MeOH (1.5 mL), and Pd/C (20 mg, 0.009) was added. The reaction mixture was stirred under H_2 atmosphere for10 h at ambient temperature, filtered through celite then concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 50-85% CH_3CN 0.1% TFA) to yield *N*-((3-(aminomethyl)phenyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-

dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (**84**, 27 mg, 0.040 mmol) as a colorless amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.93 (t, *J* = 5.9 Hz, 2H), 7.78 (s, 1H), 7.76 - 7.67 (m, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.58 - 7.49 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.76 (s, 2H), 4.56 (d, *J* = 5.9 Hz, 2H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.77 (s, 3H), 2.79 - 2.68 (m, 2H), 2.27 (s, 6H), 2.10 - 2.03 (m, 2H), 2.00 (s, 3H), 1.94 (s, 3H); >98% at 215 nm, MS (ESI) *m/z* = 668.2 $(M+H)^+$.

To a solution of *N*-((3-(aminomethyl)phenyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (**84**, 13 mg, 0.019 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added Et_3N (5 μL, 0.038 mmol) followed by *iso*-butyryl chloride (24 μL, 1M solution in CH_2Cl_2, 0.024 mmol) and the mixture was stirred for 5 min. The reaction mixture was concentrated *in vacuo*, and the crude was purified by reverse-phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 30-85% CH_3CN 0.1% TFA) to give the title compound (12 mg, 0.016 mmol) as an off-white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.95 (t, *J* = 6.0 Hz, 1H), 7.83 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.67 - 7.64 (m, 1H), 7.63 - 7.55 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.75 (s, 2H), 4.58 (d, *J* = 6.0 Hz, 2H), 3.97 (t, *J* = 6.1 Hz, 2H), 3.77 (s, 3H), 2.80 - 2.66 (m, 2H), 2.42 (sep, *J* = 6.9 Hz, 1H), 2.27 (s, 6H), 2.09 - 2.03 (m, 2H), 2.01 (s, 3H), 1.94 (s, 3H); >98% at 215 nm, MS (ESI) *m/z* = 738.3 $(M+H)^+$.

***N*-((3-(acetamidomethyl)phenyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (67).** The title compound was prepared (8 mg, 0.011 mmol) as an off-white amorphous solid according to procedures described for compound **68** using *N*-((3-(aminomethyl)phenyl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (13 mg, 0.019 mmol), acetyl chloride (24 μL, 1M solution in CH_2Cl_2, 0.024 mmol), Et_3N (5 μL, 0.038 mmol), and CH_2Cl_2 (1 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.92 (t, *J* = 5.9 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.62 - 7.58 (m, 1H), 7.50 - 7.43 (m, 2H), 7.17 (d, *J* = 80 Hz, 1H), 6.76 (s, 2H), 4.54 (d, *J* = 5.9 Hz, 2H), 3.96 (t, *J* = 6.2 Hz, 2H), 3.77 (s, 3H), 2.82 - 2.65 (m, 2H), 2.13 (s, 3H), 2.27 (s, 6H), 2.07 - 2.02 (m, 2H), 2.00 (s, 3H), 1.94 (s, 3H); >98% at 215 nm, MS (ESI) *m/z* = 710.2 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((3-((3-methylbutanamido)methyl)phenyl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (69). The title compound was prepared (4 mg, 0.0053 mmol) as a colorless oil following the same procedure as described for compound **64** using *iso*-valeryl chloride (22 mg, 0.18 mmol). ^{1}H NMR (500 MHZ, DMSO-d_6): 10.80 (s, 1H), 8.42 (t, J = 5.5 Hz, 1H), 7.87-7.85 (m, 2H), 7.63 (d, J = 8.5 Hz, 1H), 7.56 (s, 2H), 7.19 (d, J = 8.7 Hz, 1H), 6.70 (s, 2H), 4.33 (d, J = 5.5 Hz, 2H), 3.88 (t, J = 6.5 Hz, 2H), 3.79 (s, 3H), 3.09 (t, J = 7.0 Hz, 2H), 2.25 (s, 6H), 2.01-1.89 (m, 11H), 0.79 (d, J = 6.0 Hz, 6H); >98% at 215 nm, MS (ESI) m/z = 752.1 $(M+H)^+$.

***N*-((5-(benzylcarbamoyl)furan-2-yl)sulfonyl)-6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (70).** A solution of 5-(*N*-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid (**61**, 21 mg, 0.031 mmol), phenylmethanamine (3.7 mg, 0.034 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.6 mg, 0.034 mmol) and DMAP (0.76 mg, 6.24 μmol) in CH_2Cl_2 (0.63 mL) was stirred for 15 h at ambient temperature. The reaction mixture was concentrated *in vacuo*, and the residue was purified by reverse-phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 50-90% CH_3CN 0.1% TFA) to give the title compound (9.4 mg, 0.012 mmol) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.70 (d, J = 8.5 Hz, 1H), 7.33 - 7.28 (m, 4H), 7.27 - 7.25 (m, 1H), 7.24 - 7.22 (m, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.09 - 6.82 (m, 1H), 6.65 (s, 2H), 4.63 - 4.50 (m, 2H), 4.02 (s, 3H), 3.93 (t, J = 5.6 Hz, 2H), 3.45 - 3.15 (m, 2H), 2.35 (s, 6H), 2.21 (s, 3H), 2.19 (s, 3H), 2.18 - 2.09 (m, 2H); >98% at 215 nm, MS (ESI) m/z = 762.2 $(M+H)^+$.

6-Chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-*N*-((5-((pyridin-4-ylmethyl)carbamoyl)furan-2-yl)sulfonyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxamide (71). To a solution of 5-(*N*-(6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carbonyl)sulfamoyl)furan-2-carboxylic acid (**61**, 10 mg, 0.014 mmol) in DMF (1 mL) were added pyridin-4-ylmethanamine (2.3 mg, 0.021 mmol), HBTU (11 mg, 0.028

mmol), Et_3N (8 μL, 0.056 mmol), and the mixture was stirred at ambient temperature for 10 h. The reaction was quenched by addition of H_2O (3 mL), extracted with EtOAc (3x15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by reverse-phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 30-70% CH_3CN 0.1% TFA) to give the title compound (9.4 mg, 88%) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.78 (d, *J* = 7.8 Hz, 2H), 8.08 (s, 1H), 7.64 (d, *J* = 7.1 Hz, 1H), 7.50 (d, *J* = 7.0 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.1 Hz, 1H), 6.76 (d, *J* = 7.0 Hz, 1H), 6.73 (s, 2H), 4.75 - 4.63 (m, 2H), 4.15 (t, *J* = 6.3 Hz, 2H), 3.79 (s, 3H), 2.84 - 2.69 (m, 2H), 2.27 (s, 6H), 2.09 (s, 3H), 2.02 (s, 3H), 2.00 - 1.92 (m, 2H). >98% at 215 nm, MS (ESI) *m/z* = 762.9 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((2-(isopentylamino)pyridin-4-yl)sulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (72). A solution of 2-chloropyridine-4-sulfonamide (30 mg, 0.16 mmol), 3-methylbutan-1-amine (41 mg, 0.47 mmol), pyrdine (0.040 mL, 0.47 mmol) in DMSO (0.15 mL) was heated to 150 °C in Biotage Initiator for 1 h. The reaction mixture was cooled to ambient temperature, filtered then purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 5-50% CH_3CN 0.1% TFA) to give 2-(isopentylamino)pyridine-4-sulfonamide (21 mg, 0.090 mmol) as a yellow oil. >98% at 215 nm, MS (ESI) *m/z* = 244.2 $(M+H)^+$.

A solution of 6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-7-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indole-2-carboxylic acid (40 mg, 0.08 mmol), 2-(isopentylamino)pyridine-4-sulfonamide (21 mg, 0.090 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (18 mg, 0.10 mmol) and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (1.6 mL) was stirred at ambient temperature for 16 h. The reaction mixture was concentrated, and the residue was purified by reverse phase preparative HPLC (Phenomenex Gemini C18, H_2O/CH_3CN gradient to 40-80% CH_3CN 0.1% TFA) to give the title compound (20 mg, 0.028 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.45 (brs, 1H, NH), 8.10 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.17 (brs, 1H), 6.91 (d, *J* = 5.5 Hz 1H), 6.72 (s, 2H), 3.92 (t, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 3.28 (t, *J* = 6.8 Hz, 2H), 3.13 (t, *J* = 7.4 Hz, 2H), 2.26(s, 6H), 2.01 (s, 3H), 1.99-1.93 (m, 2H), 1.93 (s, 3H), 1.65 (sep, *J* = 6.7 Hz,

1H), 1.43 (q, *J* = 7.2 Hz, 2H), 0.89 (s, 3H), 0.88 (s, 3H); >98% at 215 nm, MS (ESI) *m/z* = 725.1 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((2-(phenethylamino)pyridin-4-yl)sulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (73). The title compound was prepared as a white solid according to procedures described for preparing compound (**72**) by substituting 3-methylbutan-1-amine with phenylethan-1-amine in 46% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.55 (brs, 1H, NH), 8.14 (d, *J* = 5.5 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.30-7.17 (comp, 7H), 6.93 (d, *J* = 5.5 Hz 1H), 6.71 (s, 2H), 3.92 (t, *J* = 6.3 Hz, 2H), 3.79 (s, 3H), 3.53 (t, *J* = 7.2 Hz, 2H), 3.13 (t, *J* = 7.4 Hz, 2H), 2.85 (t, *J* = 7.4 Hz, 2H), 2.26 (s, 6H), 2.01 (s, 3H), 1.98-1.92 (m, 2H), 1.93 (s, 3H); >98% at 215 nm, MS (ESI) *m/z* = 759.1 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((2-(methyl(phenethyl)amino)pyridin-4-yl)sulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (74). The title compound was prepared as a white solid according to procedures described for preparing compound (**72**) by substituting 3-methylbutan-1-amine with N-methyl-2-phenylethan-1-amine in 74% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.80 (s, 1H, NH), 8.32 (d, *J* = 5.3 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.24-7.21 (comp, 5H), 7.16-7.12 (m, 1H), 7.10 (brs, 1H), 7.00 (dd, *J* = 5.3, 1.3 Hz 1H), 6.66 (s, 2H), 3.84 (t, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 3.75 (t, *J* = 7.8 Hz, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 3.01 (s, 3H), 2.82 (t, *J* = 7.8 Hz, 2H), 2.24(s, 6H), 2.01 (s, 3H), 1.93 (s, 3H), 1.93-1.87 (m, 2H); >98% at 215 nm, MS (ESI) *m/z* = 773.1 $(M+H)^+$.

6-chloro-3-(3-(4-chloro-3,5-dimethylphenoxy)propyl)-N-((2-((2,3-dihydro-1H-inden-2-yl)amino)pyridin-4-yl)sulfonyl)-7-(1,3,5-trimethyl-1H-pyrazol-4-yl)-1H-indole-2-carboxamide (75). The title compound was prepared as a white solid according to procedures described for preparing compound (**72**) by substituting 3-methylbutan-1-amine with N-methyl-2-phenylethan-1-amine 2,3-dihydro-1H-inden-2-amine in 61% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.61 (s, 1H, NH), 8.18 (d, *J* = 5.9 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.24-7.14 (comp, 6H), 6.96 (d, *J* = 5.4 Hz 1H), 6.71 (s, 2H), 4.59 (M, 1H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.79 (s, 3H), 3.32 (d, *J* = 7.3 Hz, 1H), 3.28 (d, *J* = 7.3 Hz, 1H), 3.13 (t, *J* = 7.5 Hz, 2H), 2.86 (d, 5.2 Hz, 1H), 2.82 (d, *J* = 5.2 Hz, 1H), 2.26

(s, 6H), 2.01 (s, 3H), 1.95 (s, 3H), 1.95-1.91 (m, 2H); >98% at 215 nm, MS (ESI) *m*/*z* = 771.1 $(M+H)^+$.